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Joint effects of diabetic-related genomic loci on the therapeutic efficacy of oral anti-diabetic drugs in Chinese type 2 diabetes patients

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Previous pharmacogenomic studies of oral anti-diabetic drugs have primarily focused on the effect of a single site. This study aimed to examine the joint effects of multiple loci on repaglinide or rosiglitazone efficacy in newly diagnosed type 2 diabetes mellitus (T2DM) patients. A total of 209 newly diagnosed T2DM patients were randomly assigned to treatment with repaglinide or rosiglitazone for 48 weeks. The reductions in fasting glucose (ΔFPG), 2h glucose (Δ2hPG) and glycated hemoglobin (ΔHbA1c) levels were significantly associated with genetic score that was constructed using the sum of the effect alleles both in the repaglinide (P=0.0011, 0.0002 and 0.0067, respectively) and rosiglitazone cohorts (P=0.0002, 0.0014 and 0.0164, respectively) after adjusting for age, gender, body mass index and dosage. Survival analyses showed a trend towards a greater attainment rate of target HbA1c level in individuals with a high genetic score in the repaglinide cohort and rosiglitazone cohort (Plog-rank=0.0815 and 0.0867, respectively) when the attainment of treatment targets were defined as more than 20% decrease of FPG, 2hPG, and HbA1c levels after treatment. In conclusion, we identified the joint effects of several T2DM-related loci on the efficacy of oral anti-diabetic drugs; moreover, we built a model to predict the drug efficacy.
OL04-2
A causal relationship between uric acid and diabetic macrovascular disease in Chinese type 2 diabetes patients: A Mendelian randomization analysis

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Background: As the association between uric acid and macrovascular disease has been heavily debated, we aimed to confirm whether there is a causal relationship between uric acid and diabetic macrovascular disease through Mendelian randomization analysis.

Methods: In 3,207 type 2 diabetes patients, seventeen SNPs (single nucleotide polymorphisms) related to uric acid were genotyped. A weighted GRS (genetic risk score) was calculated using selected SNPs and the strength of their effects on uric acid levels. Diabetic macrovascular disease was diagnosed through vascular ultrasound, magnetic resonance imaging or other clinical evidence. Associations of diabetic macrovascular disease with uric acid and weighted GRS were evaluated separately.

Results: In total participants and among females, the prevalence of diabetic macrovascular disease was significantly higher in hyperuricemic group than in normouricemic group, and uric acid was associated with diabetic macrovascular disease (OR=1.068, p=0.0349; OR=1.122, p=0.0158). The prevalence of diabetic macrovascular disease increased with the weighted GRS in a J-shaped manner for the females. The weighted GRS was positively correlated with uric acid in total population, male patients and female patients (β=0.203, p<0.0001; β=0.255, p<0.0001; β=0.142, p<0.0001, respectively). The weighted GRS was significantly associated with diabetic macrovascular disease in female patients (OR=1.184, p=0.0039). Among females, the observed association between weighted GRS and diabetic macrovascular disease was greater than predicted.

Conclusions: Using the uric acid-related weighted GRS as an instrumental variable for Mendelian randomization analysis, our study provided an evidence for the causal relationship between uric acid and diabetic macrovascular disease in Chinese females with type 2 diabetes.
The association of GIPR variants with fat accumulation in Chinese Han populations

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Objectives
Obesity, particularly central obesity which is considered as the culprit of obesity-associated complications such as type 2 diabetes, metabolic syndrome and cardiovascular disease, imposes serious medical and economic burdens. Compared with body mass index (BMI), waist circumference and waist to hip ratio, visceral fat area (VFA) and subcutaneous fat area (SFA) is more precise as a measurement of obesity. Genetic variants of glucose-dependent insulinotropic polypeptide receptor (GIPR) relevant to BMI and glucose metabolism have been uncovered using genome-wide association studies (GWAS). We aimed to test the association of GIPR with fat distribution in Chinese Han populations.

Methods
A total of 2884 community-based individuals with Chinese Han ancestry were genotyped for four tag single-nucleotide polymorphisms (SNPs) of GIPR. Linear analysis was applied to test the associations of these variants with VFA and SFA quantified by Magnetic Resonance Imaging (MRI) as well as glucose related traits.

Results
We replicated the effects of several loci of GIPR on BMI, waist circumference as well as glucose related traits in Chinese Han populations (P range from 9.46×10^-5 to 0.028). In the search for fat distribution variants, we found rs11671664 in GIPR was associated with VFA and SFA in total subjects (p=0.018 and 0.020, respectively). In a subgroup analysis stratified by gender, rs11671664 showed the association with VFA in males (p=0.030), whereas displayed the borderline association with SFA in females (p=0.049). However, after adjusting for BMI, the association disappeared. Analysis of linkage disequilibrium (LD) revealed no association between the GIPR haplotype block (rs2334255 and rs2287019) and fat distribution, while we observed that the GT and GC haplotypes of rs2334255 and rs2287019 were associated with higher glucose and insulin level as well as higher insulin sensitivity assessed with Gutt index (P range from 1.90×10^-5 to 0.045).

Conclusion
Our results suggest that the association between rs11671664 and visceral fat distribution might be mediated by BMI in Chinese Han populations.

Key words: Single-nucleotide polymorphisms, GIPR, fat accumulation, BMI, glucose metabolism, Chinese
Impaired pancreatic beta cell compensatory function is the main cause of type 2 diabetes in individuals with high genetic risk

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Aims/hypothesis

We aimed to evaluate the combined effects of type 2 diabetes risk variants on predicting deterioration of blood glucose and progression of beta cell function and insulin sensitivity in a 9-year prospective cohort from the Chinese population.

Methods

We constructed a weighted genetic risk score (GRS) model based on 40 variants associated with type 2 diabetes validated in an established cross-sectional Chinese population (n=6,822). The weighted scores were categorised into tertiles to assess the predictive capacity for incidence of type 2 diabetes and impaired glucose regulation (IGR), as well as for changes in Stumvoll first- and second-phase insulin secretion indices and Gutt’s insulin sensitivity index (ISI) in a community-based 9-year prospective cohort (n=2,495), including 2192 individuals with normal glucose tolerance and 303 with IGR at baseline, through logistic and multiple linear regression tests.

Results

Weighted GRS predicted the incidence of type 2 diabetes and IGR in logistic regression (OR 1.236, 95% CI 1.100, 1.389, p=0.0004) after adjusting for age, sex, BMI, smoking and alcohol status at baseline. Moreover, we observed that weighted GRS was able to predict deterioration in beta cell function ($\beta=-0.0480$, p=9.66×10^{-5} and $\beta=-0.0303$, p=3.32×10^{-5} for first- and second-phase insulin secretion, respectively), but not insulin sensitivity (p=0.3815), during the 9-year follow-up period.

Conclusions/interpretation

The weighted GRS predicted blood glucose deterioration arising from change in beta cell function in the Chinese population. Individuals in the intermediate- or high-weighted GRS group exhibited progressive deterioration of beta cell function.
Computational analysis of type 2 diabetes associated SNPs and genes identified by GWASs

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Type 2 diabetes (T2D) is characterized by chronic hyperglycemia due to insulin resistance of peripheral tissues and insufficient compensatory insulin secretion by pancreatic beta cells. Until 2007, genetic study of T2D was mainly achieved by genome-wide familial linkage analyses and candidate gene association studies with limited success. Progress in identifying common variants associated with T2D has since been accelerated primarily by Genome-wide association studies (GWASs). By the end of 2014, 43 GWASs and 13 meta-analyses reported 116 genes and 161 SNPs (Lead SNP) that were associated with T2D at the stringent threshold of 5×10⁻⁸ for genome-wide significance. Functional characterization and mechanistic elucidation of these SNPs and genes action are the next major challenge. We conducted multiple computational analyses to explore function and mechanisms of T2D GWAS-associated SNPs and genes, including SNP conservation analysis and functional annotation (influence of SNPs on protein phosphorylation and miRNA binding, eQTLs), gene ontology analysis, pathway enrichment analysis and protein-protein interaction analysis.

Functional annotations using GWAS3D and RegulomeDB show that most of the SNPs were located in the non-coding region with multiple regulatory functions. Thirty-eight lead SNPs had the long-range regulatory signals. Comparative genomic analyses showed that 9 SNPs are highly conserved. A total of 1174 proxy SNPs (r² ≥ 0.80) were identified by SNAP based on genotype data from the International HapMap Project(v3) and the 1000 Genomes Pilot 1 Project with the CEU population panel. Some T2D GWAS associated SNPs were located at protein binding sites (identified through CHIP-seq), including CTCF, EP300, HNF4A, TCF7L2, FOXA1 and FOXA2, which are required for normal pancreatic development and maintaining β-cell function. Two T2D GWAS lead SNPs and 29 proxy SNPs were identified as miRNA related SNPs (miR-SNPs) that might influence the binding of miRNAs, and 4 T2D lead SNPs and 8 proxy SNPs were identified as PhosSNPs that might affect protein phosphorylation. The effect of these T2D-associated GWAS SNPs on miRNAs and transcription factor binding are currently being experimentally tested in our lab.

GO analysis showed that most of the T2D related genes were enriched in the biological regulation process and binding function. Pathway enrichment analysis confirmed 2 well-known maturity onset diabetes of the young and T2D pathways. PPI network analysis identified highly interconnected “hub” genes TCF7L2, MTNR1B, SLC30A8, CDKAL1, IGF2BP2, CDC123 and KCNJ11 and FTO, HHEX and HNF1B THADA, JAZF1, CAMK1D and WFS1 and TSPAN8 that created 2 tight subnetwork
OL04-6

Association between GWAS-identified variants with CKD in Chinese with Type 2 Diabetes: The Hong Kong Diabetes Registry

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Background and objectives:
Chronic kidney disease (CKD) is an important complication in patients with diabetes and significant heritability has been noted. Recent genome-wide association studies (GWAS) have identified a number of single nucleotide polymorphisms (SNPs) associated with CKD and renal function traits. However, the majority of these variants were identified from studies involving Caucasians and African Americans, with few studies conducted in Asians or involving patients with diabetes. We conducted a replication study to examine whether these SNPs are associated with the risk of developing CKD in Chinese patients with type 2 diabetes (T2D).

Subjects and methods:
We performed a nested case-control study within the Hong Kong Diabetes Registry. Genome-wide genotyping was conducted for each subject using the Illumina Omni 2.5+ exome array and genotype data was imputed using minimac 3 with the 1000 Genomes Project phase 3 v5 as reference panel. After standard quality control, a total of 5730 Chinese type 2 diabetic patients were included, including 2881 patients with pre-existing or incident CKD, and 2849 free of CKD. Through literature review, a total of 77 GWAS-identified SNPs were retrieved from previous publications as being significantly associated with CKD or renal function traits. We conducted in silico look-up to investigate associations between these known SNPs and CKD in T2D utilizing logistic regression and an additive model.

Results:
The mean age of all subjects was 57.5 ± 12.9 years, 45.7% male, median duration of diabetes was 6 [interquartile range: 2-11] years, and 29% had diabetic retinopathy at baseline. After adjustment for age, gender and principal components, among the 77 known SNPs, the directly-genotyped variant rs881858 near VEGFA (OR=0.886, 95% CI 0.805-0.974, P=0.012) was significantly associated with CKD in Chinese T2D patient. An imputed SNP rs266734 also showed significant association with CKD (OR=0.695, 95% CI 0.522-0.925, p=0.012). The observed effect was consistent with the direction from previous reported findings. Excluding 8 SNPS with poor quality of imputation, the remaining 67 SNPs did not exhibit significant associations with CKD in Chinese with T2D.

Conclusions:
Among 77 known GWAS-identified SNPs for kidney diseases, we identified significant association between rs881858 and CKD in Chinese patients with T2D. The discrepancies may be related to different ethnicity as well as the group of subjects being studied (general population vs. subjects with T2D). Our results highlight the need to perform studies in the relevant ethnic group in order to uncover the genetic susceptibility of diabetic kidney disease.
Genome-wide association study in Chinese identifies new susceptibility loci associated with chronic kidney disease in type 2 diabetes

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Background and aims:
Diabetic kidney disease is a major complication of diabetes and the leading cause of end-stage renal disease in most parts of the world. Although a few common susceptibility variants have been identified by several genome-wide association studies (GWAS) recently, much of the inherited predisposition to diabetic kidney disease remains unexplained. To unravel the genetic basis of this important complication, we performed a nested case-control study for chronic kidney disease (CKD) in type 2 diabetes (T2D) from the Hong Kong Diabetes Registry (HKDR).

Materials and methods:
More than 8,000 patients with T2D and prospective follow-up were included in the HKDR. eGFR was calculated according to the Chinese Modification of Diet in Renal Disease (MDRD) equation. CKD was defined (i) Diabetes with renal manifestations (ICD-9 code: 250.4), chronic kidney disease (ICD-9 code: 585), or unspecified renal failure (ICD-9 code: 586) or (ii) dialysis (ICD-9 procedure code: 39.95) or peritoneal dialysis (ICD-9 procedure code: 54.98) or (iii) eGFR < 60 ml/min per 1.73 m2 during follow-up period. Samples were genotyped using the Illumina Omni 2.5+ exome array and genotype data was imputed using minimac 3 with the 1000 Genomes Project phase 3 v5 as reference panel. After standard quality control, ~8 million common SNPs were included in the final analysis. Association analysis was adjusted for age, gender, and principal components.

Results:
After sample QC, we included 2881 case subjects with T2D and CKD, and 2849 control subjects with T2D duration of >10 years but free of CKD in the genome-wide association analysis (mean age of all subjects 57.5 ± 12.9 years, 45.7% male, median duration of diabetes 6 [interquartile range: 2-11] years, and 29% with retinopathy at baseline). We identified 22 SNPs with suggestive association with CKD in T2D (p<10^{-5}), with one of the strongest signal from a SNP on chromosome 9, OR 0.73 (95% CI 0.65-0.83, p=9.98×10^{-7}), with other top suggestive association signals from loci on chromosomes 1, 2, 4, 7, 11, 14, 16, 17, 18, 19.

Conclusions:
Our study has identified a number of novel regions associated with CKD in T2D. Additional genotyping and integrative analysis together with methylation data are currently in progress.

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Identification of a mutation associated with early-onset diabetes in the intron of INS gene with whole-exome sequencing.

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Whole-exome sequencing is a new technology for mutation detection in genetic disorders. We explored the gene responsible for a family with early-onset diabetes using this method. In the family, the proband was diagnosed with hyperglycemia at the age of 3 years and has been treated with insulin immediately after diagnosed. Her two daughters were also diagnosed with hyperglycemia at the age of 12 months and 18 months, respectively. They have been also treated with insulin immediately after diagnosed. All exons and flanking regions of human genome shown in the consensus coding sequence project database were captured with specific probes (Agilent SureSelect XT Human All Exon V4 kit) and the products were sequenced with next generation sequencer (HiSeq2000). The generated reads were annotated with reference sequences in UCSC Genome Brower hg19 and two databases of variants (dbSNP 135 and 1000 Genomes). We checked the result for twenty-six known early-onset diabetes (MODY and/or neonatal diabetes) genes and a heterozygous intronic mutation c.188-31G>A in the INS gene, which is not registered in two databases, was identified in the genomic DNA of the proband. The mutation was also identified in her two daughters, but not in her son without diabetes. The substitution is located 31 bp proximal from exon 3 in the intron 2 of the INS gene. It is predicted to create an ectopic splice site leading to insert 29 nucleotides of intron 2 as exonic sequence in the transcript. The abnormal insulin would induce pancreatic beta cell apoptosis by the endoplasmic reticulum stress. This mutation has been previously described in three reports for analyzing the gene of neonatal diabetes. Our result suggests that the intronic mutation c.188-31G>A is a hot spot of causal mutation for diabetes in the INS gene.